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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/267,963	03/12/99	MIYAZONO K	LUD-5539.1-C

EXAMINER	
ROMEO,D	
ART UNIT	**PAPER NUMBER**
1647	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/267,963	Miyazano et al.
Examiner	**Art Unit**
David Romeo	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *20 Jun 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *14-20 and 28* is/are pending in the application.

4a) Of the above, claim(s) *17-20* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14-16 and 28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *14-20 and 28* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of group III, claims 14, 15, 17, 18, 20, 28 in Paper No. 17 is acknowledged. Upon further consideration the restriction requirement set forth in the paper mailed 05/21/01 (Paper No. 15) is withdrawn. The restriction requirement set forth in the paper mailed 04/27/00 (Paper No. 6) is recast below.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 14-16, 28, to the extent that they are drawn to a method of inhibiting Smad1 or Smad5 phosphorylation using an antibody which binds to TGF-β, classified in class 530, subclass 388.22.

II. Claims 14, 15, 17, 28, to the extent that they are drawn to a method of inhibiting Smad1 or Smad5 phosphorylation using an antibody that binds ALK-1, classified in class 530, subclass 388.23.

III. Claims 14, 18, 19, 28, to the extent that they are drawn to a method of inhibiting Smad1 or Smad5 phosphorylation using Smad6, classified in class 530, subclass 350.

IV. Claims 14, 18, 19, 28, to the extent that they are drawn to a method of inhibiting Smad1 or Smad5 phosphorylation using Smad7, classified in class 530, subclass 350.

V. Claims 14, 20, to the extent that they are drawn to a method of inhibiting Smad1 phosphorylation using an indeterminate inhibitor that inhibits the interaction of Smad1 with a type II TGF-β receptor, indeterminate class and subclass.

3. The inventions are distinct, each from the other because of the following reasons:

The following pairwise combinations of methods are independent and distinct, wherein each member of a pair performs different functions, using different starting materials and/or process steps and/or with different outcomes: I and each of II-V; II and each of III-V; III and each of IV-V; IV and each of V.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

5. Because these inventions are distinct for the reasons given above and the searches required are not coextensive, restriction for examination purposes as indicated is proper.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. Applicant's election of group III, claims 14-20, 28, to the extent they read on methods which inhibit Smad1 or Smad5 phosphorylation and election of an antibody which binds TGF-β as the species in Paper No. 7 has constructively elected group I above, claims 14-16, 28, for prosecution on the merits. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

8. Claims 17-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

9. Claims 14-16, 28 are being examined only to the extent they read upon the elected invention.

10. Newly submitted claim 28 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly submitted claim 28 is directed to the activation of ALK-1. The invention originally claimed is presumably directed to the inhibition of Smad1 or Smad5 phosphorylation. Each of the methods are independent and distinct, wherein each performs different functions, using different starting materials and/or process steps and/or with different outcomes.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 28 is withdrawn from consideration to the extent that it is directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

11. The communication filed 03/08/2001 is not fully responsive to the Office communication mailed 08/15/2000 (Paper No. 9) for the reason(s) set forth on the Notice To Comply With The Sequence Rules and Raw Sequence Listing Error Report attached to the Office communication mailed 06/06/01 (Paper No. 16).

12. Figure 3 is presented on separate panels. 37 C.F.R. § 1.84 (u) (1) states that partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. View numbers must be

preceded by the abbreviation "FIG." Thus, the separate panels should be renumbered FIG. 3A, FIG. 3B, etc. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u) (1), the Brief Description of the Drawings and the rest of the specification must be amended accordingly. It is acknowledged that Applicants will provide an amended Figure 3 upon receiving a notice of allowance.

13. Claims 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi (u9)[1]. Applicants argue that the examiner has not provided any objective evidence in support of the rejection and that probabilities or possibilities are not sufficient to establish inherency. Applicants' arguments have been fully considered but they are not persuasive. As one of ordinary skill in the art would appreciate an anti-TGF-β1 neutralizing antibody is an antibody that binds to TGF-β1. Claim 16 of the instant application is objective evidence that "an antibody which binds to TGF-β" is "an inhibitor which interferes with phosphorylation of Smad1". Further, an HUVEC is a cell which presents ALK-1 on its surfaces and the specification at page 35, lines 22-23, is objective evidence of this fact. Insofar as an HUVEC is a cell which presents ALK-1 on its surfaces and insofar as TGF-β binds to ALK-1 leading to phosphorylation of Smad1 (see the instant

[1]References cited by the examiner are in an alphanumeric format, such as "a1", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

specification at page 37, lines 26-27, for objective evidence of this fact) then an HUVEC is a cell which expresses said gene. "Inhibiting expression of a gene" is an intended use of the claimed method and has not been accorded any patentable weight. Further, Takahashi teaches the sole process step of the claimed method, which is contacting a cell with an inhibitor. Although the inhibitor has the property of interfering with phosphorylation of Smad1, the claims do not require that phosphorylation of Smad1 be interfered with as a result of this contact.

New formal matters, objections, and/or rejections:

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 14, 15, 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to or encompass an "inhibitor" which interferes with the phosphorylation of Smad1 or an "agent" which inhibits ALK-1. There are no structural limitations to the "inhibitor" or "agent". The claims are thus generic claims encompassing any and all such "inhibitors" or "agents". The specification teaches antibodies that bind either TGF-β1 or

ALK-1, and Smad-6 or -7. The description of such antibodies is not a description of any and all such "inhibitors" or "agents" because there is no requirement that such "inhibitors" or "agents" be antibodies or that they even be proteinaceous in nature. Smad-6 or -7 are unlike any and all such "inhibitors" or "agents" because firstly, Smad-6 or -7 are intracellular proteins and there is no requirement that such "inhibitors" or "agents" be proteinaceous in nature, and, secondly, because the specification lacks a description of contacting a cell extracellularly with an intracellular protein such that the protein gains access to the intracellular compartment and exerts its desired effect nor is such a process consonant with the original disclosure. At best it might be obvious to the skilled artisan that it would be desirable to employ the disclosed materials and methods in a screening process in an attempt to identify such "inhibitors" or "agents". However, the written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one is in possession of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious.

16. Claims 14, 15, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds the extracellular domain of ALK-1 and blocks the TGF-β1-mediated induced phosphorylation of Smad-1 thereby, does not reasonably provide enablement for an "inhibitor" or "agent". The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed to or encompass an "inhibitor" which interferes with the phosphorylation of Smad1 or an "agent" which inhibits ALK-1. There are no structural limitations to the "inhibitor" or "agent". The claims are thus generic claims encompassing any and all such "inhibitors" or "agents" that achieve the desired effect. The limitations "inhibitor" or "agent" are analogous to a single means type of claim. A single means claim, i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. The problem with the phrase "inhibitor" or "agent" is that it covers every conceivable means which achieves the desired activity, whereas the specification discloses at most antibodies that bind either TGF-β1 or ALK-1, and Smad-6 or -7. As such, the terms "inhibitor" or "agent" encompass compounds that are structurally unrelated to either an antibody, Smad-6, Smad-7, or even a protein. Furthermore, Smad-6 or -7 are unlike any and all such "inhibitors" or "agents" because firstly, Smad-6 or -7 are intracellular proteins and there is no requirement that such "inhibitors" or "agents" be proteinaceous in nature, and, secondly, because the specification lacks a description of contacting a cell extracellularly with an intracellular protein such that the proteins gains access to the intracellular compartment and exerts its desired effect nor is such a process consonant with the original disclosure. The specification fails to teach the skilled artisan how to make such structurally unrelated compounds that have the desired activity or will perform

in the manner instantly disclosed. Furthermore, the instant specification does not identify those structural features of an "inhibitor" or "agent" which are essential for the desired activity those which are not. In the absence of this information a practitioner would have to resort to a substantial amount of unduly extensive and fundamentally unpredictable experimentation in the form of random analysis of any and all "inhibitors" or "agents" before they could even begin to rationally make an "inhibitor" or "agent" other than an antibody that binds ALK-1. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 14, 15 are indefinite because claim 14 lacks a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved. The intended use of the claimed method is "inhibiting expression of a gene". However, an intended use is not the same as achieving inhibition of gene expression. The sole process step recites contacting a cell with an inhibitor. The inhibitor has the property of interfering with phosphorylation of Smad1. However, the claims do not require that phosphorylation of Smad1 be interfered with as a result of this contact. It is unclear if phosphorylation of Smad1 is interfered with as a result of this contact. Furthermore, the claims do not require that the "contact" result in the inhibition of gene expression. It is unclear what result of the process can be inferred. The metes and bounds of the claim(s) are not clearly set forth.

b. Claim(s) 28 is indefinite over the recitation of the term "inhibits ALK-1" because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "inhibits ALK-1". An artisan cannot determine what additional limitations are placed upon a claim by the presence of this term. The metes and bounds of the claim(s) are not clearly set forth. For the purposes of examining all issues related to the patentability of the instant invention the term "inhibits ALK-1" has been interpreted to mean inhibits the phosphorylation of Smad1 or Smad5.

c. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted steps are: an agent, compound, or substance that phosphorylates Smad1 or Smad5. In the absence of the phosphorylation of Smad1 or Smad5 and the activation of gene expression thereby there would be no detection of a difference in gene expression.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kokame (w9) in view of Hopkins (u18) and Kurihara (v18). Kokame teaches that an elevated level of homocysteine is associated with arteriosclerosis and thrombosis. Kokame uses differential display to study the mechanisms by which homocysteine may promote vascular diseases. See abstract. The differential display technique involves comparing transcripts from a first sample of cells in the absence of a stimulus with transcripts from a second sample of cells in the presence of the stimulus, wherein any difference there between are transcripts whose activation is effected by the stimulus. See page 29660. It is apparent from Kokame that HUVECs are a model to be used for in vitro studies of vascular disease. Studies of novel gene transcripts are required to reveal the

underlying mechanisms of homocysteine-induced vascular injury (page 29665, column 1, full paragraph 1). Kokame does not teach a method of identifying a gene whose activation is effected by TGF-β comprising contacting a first sample of HUVECs with platelet lysates, removing transcripts of said cells, and comparing said transcripts with transcripts from a second sample of HUVECs contacted with platelet lysates in the presence of neutralizing antibodies to TGF-β.

Hopkins teaches the platelet release reaction is an integral part of thrombosis. PAI-1 has been identifies in endothelial cells, hepatocytes, smooth muscle cells, and fibroblasts among other cell types and platelets are richly endowed with TGF-β (page 239, right column, full paragraph 1). Hopkins teaches a method of identifying a gene whose activation is effected by TGF-β comprising contacting a first sample of cells with platelet lysates and measuring the increase in PAI-1 protein and comparing this level of PAI-1 protein with the level of PAI-1 protein produced by a second sample of cells contacted with platelet lysates and neutralizing antibodies to TGF-β. See Abstract.

Kurihara teaches that TGF-β is related to thrombus formation (Abstract).

Hopkins and Kurihara do not teach a method a method of identifying a gene whose activation is effected by TGF-β comprising contacting a first sample of HUVECs with platelet lysates, removing transcripts of said cells, and comparing said transcripts with transcripts from a second sample of HUVECs contacted with platelet lysates in the presence of neutralizing antibodies to TGF-β.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use HUVECs and differential display to study the mechanisms by which homocysteine may promote vascular diseases, as taught by Kokame, and to modify that teaching by using platelet lysates in the presence and absence of anti-TGF-β neutralizing antibodies, as taught by Hopkins, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to study the role of TGF-β-induced novel gene transcripts underlying mechanisms of platelet-derived-TGF-β-induced vascular injury or diseases such as thrombosis. The properties that Applicants claim or disclose would naturally flow from the teachings of Kokame in view of Hopkins and Kurihara because HUVECs are cells which express ALK-1 and which express and phosphorylate Smad1 or Smad5, an anti-TGF-β neutralizing antibody is an agent that inhibits ALK-1, wherein "inhibits ALK-1" has been interpreted to mean inhibits TGF-β-ALK-1 binding and the phosphorylation of Smad1 or Smad5 thereby, and any differences in transcripts between the presence and absence of neutralizing antibodies to TGF-β are transcripts of genes whose activation is effected by phosphorylation of Smad1 or Smad5. The invention is prima facie obvious over the prior art.

Applicants arguments with respect to Hopkins and Kokame have been considered but they are moot in view of the new grounds of rejection above.

Conclusion

21. No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

OFFICIAL PAPERS FILED BY FAX SHOULD BE DIRECTED TO (703) 308-4242.

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

SEPTEMBER 7, 2001